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## Cardiac background sodium current: elusive but important.

Hongwei Cheng PhD <sup>1</sup>, Andrew F. James DPhil <sup>1</sup>, Mark R. Boyett PhD, FRSB, FRCP(hon)<sup>2</sup>, Jules C. Hancox PhD, FRSB, FBPhS<sup>1\*</sup>

*<sup>1</sup> School of Physiology, Pharmacology & Neuroscience  
Biomedical Sciences Building,  
University of Bristol,  
Bristol BS8 1TD, UK*

*<sup>2</sup> Institute of Cardiovascular Sciences,  
University of Manchester,  
Core Technology Facility,  
46 Grafton Street,  
Manchester, M13 9NT, UK*

\* Corresponding author. Tel.: +44-1173312292; E-mail address: [jules.hancox@bristol.ac.uk](mailto:jules.hancox@bristol.ac.uk)  
(Jules C. Hancox).

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The intrinsic rhythmicity of the heart resides in the specialized pacemaker-conduction system: the spontaneous rate of the primary pacemaker, the sinoatrial node (SAN), normally dominates and therefore sets the heart rate. Under conditions of SAN failure or impaired conduction, the atrioventricular node (AVN), which can also generate spontaneous activity, can take over pacemaking of the ventricles. After over fifty years' study of the mechanisms of cardiac pacemaking, present knowledge points to the existence of both membrane and calcium ( $\text{Ca}^{2+}$ ) "clocks", which function together to generate pacemaker activity and mediate the effects autonomic nervous system modulation <sup>1</sup>. Multiple channels contribute to the membrane clock, with the hyperpolarisation activated current,  $I_f$ , having been the focus of particular attention; the  $\text{Ca}^{2+}$  clock involves rhythmic release of  $\text{Ca}^{2+}$  from the SR via ryanodine receptors and ionic current generation *via* the sarcolemmal Na-Ca exchange.

The presence of multiple overlapping contributors to cardiac pacemaking makes evolutionary sense, potentially allowing for some redundancy in an important system<sup>2</sup>. In the SAN, for example,  $I_f$  and "background" sodium ( $\text{Na}^+$ ) current may act together to stabilize SAN cell pacemaking <sup>3</sup>. Background  $\text{Na}^+$  current in rabbit SAN cells was first isolated and characterized by Hagiwara *et al* in 1992 <sup>4</sup>. They reported a  $\text{Na}^+$ -dependent inward current,  $I_{B,Na}$ , flowing through cation channels with poor monovalent selectivity, which exhibited Goldman-Hodgkin-Katz (GHK) voltage-dependence and partial sensitivity to a high (1 mM) concentration of amiloride <sup>4</sup>. In a subsequent SAN cell simulation study, Noble and colleagues argued that reduction of  $I_{B,Na}$  led, *via* membrane hyperpolarization, to recruitment of more  $I_f$  and that the converse applied when  $I_{B,Na}$  was increased – with the two currents thus acting reciprocally to stabilize pacemaking rate of SAN cells <sup>3</sup>. By contrast, a later study reported a dominant role for  $I_{B,Na}$  during SAN diastolic depolarization <sup>5</sup>. Overall, however,  $I_{B,Na}$  has been somewhat under-investigated, most likely because of (i) the lack of a molecular correlate of the underlying channel and (ii) an inability selectively to inhibit the current whilst measuring action potentials, confounding the ability to assess its role(s) experimentally.

This year, attention has again been drawn to  $I_{B,Na}$  through work on cells from the heart's secondary pacemaker, the AVN <sup>6</sup>. Using conditions which inhibited major voltage and time-dependent conductances, Cheng and colleagues have isolated  $I_{B,Na}$  for the first time from AVN cells of two model species (rabbit and mouse) <sup>6</sup>. AVN  $I_{B,Na}$  is time-independent, shows GHK voltage-dependence and closely resembles that reported for the SAN <sup>4, 6</sup>. The underlying channels show poor monovalent cation selectivity with an Eisenmann III ( $Rb^+ > K^+ > Cs^+ > Na^+ > Li^+$ ) permeability sequence. To our knowledge, this new study also provides, for the first time for any cardiac region, an estimate of single channel conductance for the non-selective cation channels (NSCCs) mediating  $I_{B,Na}$ . This was obtained through the use of "noise" analysis of the difference current between  $Na^+$ -containing and  $Na^+$ -free conditions, producing a value of  $3.2 \pm 1.2$  pS (mean  $\pm$  standard error) with 95% confidence intervals of 0.9 to 5.5 pS. AVN  $I_{B,Na}$  was found to be partially sensitive to inhibition by lanthanides ( $Gd^{3+}$ ,  $La^{3+}$ ), ruthenium red, amiloride (at 1 mM), and low extracellular pH, but was insensitive to flufenamic acid <sup>6</sup>. None of these interventions is anticipated to be  $I_{B,Na}$ -selective under physiological recording conditions. In subsequent experiments the NSCC inhibitor SKF-96365 was investigated as a tool to study  $I_{B,Na}$ ; however, whilst this compound does partially inhibit  $I_{B,Na}$  it also blocks voltage dependent  $Ca^{2+}$  and  $K^+$  currents in AVN cells <sup>7</sup>. Without selective pharmacology, the only way to interrogate the role(s) of  $I_{B,Na}$  is through computer modelling and Cheng *et al* used both single cell and simplified strand AVN models to study role(s) of the current in the AVN. In a spontaneously active single cell model, removal of  $I_{B,Na}$  led to quiescence <sup>3</sup>, consistent with a significant role in AVN cell pacemaking. Removal of  $I_{B,Na}$  from cells in a 1D strand did not alter the shape of stimulated action potentials, but slowed conduction (by ~20%) <sup>6</sup>.

The new study by Cheng *et al* <sup>6</sup> shows clearly that AVN cells from the pacemaker-conduction system possess a robust  $I_{B,Na}$ , which is mediated by NSCCs of low single channel conductance. However, although the study extends the list of agents that are partial inhibitors of  $I_{B,Na}$ , there is still no selective pharmacological inhibitor of these channels. The simulation data are strongly suggestive of a physiologically significant role for  $I_{B,Na}$  in the AVN, but it is not yet possible to validate these findings pharmacologically. A molecular approach to investigating channel function is desirable in such circumstances; however the

combination of ion permeability sequence, single channel conductance and observed pharmacology of  $I_{B,Na}$  are difficult to reconcile with those of a single NSCC with (a) known molecular correlate(s). This suggests that either the channels underlying  $I_{B,Na}$  are entirely distinct from known NSCCs, or that they are comprised of known NSCC proteins, but of somehow modified conductance/permeability. The importance of  $I_{B,Na}$  to AVN function highlighted in the study by Cheng and colleagues<sup>6</sup> highlights a need not to overlook this cardiac current and that the identification of the molecular basis of the channels mediating  $I_{B,Na}$  is of great importance to the ability further to interrogate its role in the heart.

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